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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,405	SIDELMAN, ZVI	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/1/10 &10/30/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *191-269* is/are pending in the application.

4a) Of the above claim(s) *191-246 and 250-264* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *247-249* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 191-269 are pending.

The preliminary amendment filed 10/30/07 which cancels claims 1-190 and 193-221, and adds claims 240-269 has been entered.

Claim benefit

Applicant's claim for the benefit of a prior-filed application 60548401 filed 3/1/04 under 35 U.S.C. 119(e) is acknowledged. 60548401 has full support for the elected invention (see below).

Election/Restrictions

Applicants' election filed 7/1/10 of Group 5, claims 247-249, and additional election of "SEQ ID NO:27" (from claim 247), "hematopoiesis" (from claim 248) and "thrombopoietin" (from (claim 249) instant with traverse is acknowledged. The traverse is on the ground(s) that search SEQ ID NOs:28-30 together with the elected SEQ ID NO:27 would not be an unduly difficult or time, i.e., burden to Examiner. The amino acid sequences of SEQ ID NOs:27 and 28 are derived from β-casein (p.40, line 10, the specification); wherein SEQ ID NO:27 (17 amino acids, "193-209 of β-casein", see page 76, lines 23-24, the specification) differs from SEQ ID NO:28 (16 amino acids, "193-208 of β-casein", page 101, line 20, the specification) in that they are identical except SEQ ID NO:27 has additional C-terminal residue "Val". Thus, SEQ ID NOs:27 and 28 are obvious variation from each other and therefore are examined together.

However, SEQ ID NOs:29 and 30 are distinct from SEQ ID NO:27 or 28 in amino acid sequences; SEQ ID NO:27 (17 amino acids) is neither fragment of SEQ ID NO:29 (64 amino

acids) nor fragment of SEQ ID NO:22 (22 amino acids). Thus, SEQ ID NOs:29 and 30 are patentably distinct from the elected SEQ ID NO:2; examining them requires different sequence and art searches, and thus is the burden to examiner. SEQ ID NOs:29 and 30 are therefore, not examined in this Office action.

Claims 191-246 and 250-264 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Therefore, claims 247-249, SEQ ID NO:27, the elected "hematopoiesis" (referring to formation of blood cells or/and blood cellular components), and thrombopoietin are under examination.

Objection to specification

The disclosure is objected to because of the following informalities:

(1) The continuing data of the specification needs to be updated.

(2) At page 28, line 17-18, "SEQ ID No." should be changed to "SEQ ID NO:" for consistence. Similar changes should be made throughout the specification.

(3) At page 22-23, the brief description for Figure 3 needs to the meanings of "$FICD_3$" and "FICD56".

(4) At page 25, the brief description for Figure 9 needs to clarify the meanings of "10ex3" and "mmex3" shown in this figure.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2).

However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

In Figure 26a-26b, Figure 26b-26c, Figure 26c-26d, Figure 26d-26e, Figure 26e-26f, Figure 26f-26g, Figure 26g-26h, and Figure 26h-26i, he sequences of 25 amino acid sequences (from "RP" to "RPKHP IKHQGLP QEVLNENLLRFFVA" of αS1-peptides as listed in the left column of each figure stated above) is disclosed without SEQ ID NO identification.

Objection to drawings

The drawings are objected to because in Figure 26a, the "column" showing a "table" consisting of "Fig.26a", "Fig.26b" , "Fig.26c", Fig.26d" , "Fig.26e", "Fig.26f", "Fig.26g", "Fig.2a" and "Fig.26i" should be delete since said "column" does not have patentable input for Figure 26.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet"

pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. Alternatively, the specification could be amended to describe the subpanels.

The objection to the drawings will not be held in abeyance.

Objection to claims

Claim 247-249 is objected to because claim 247 contain the non-elected (not species) SEQ ID NOs:29-4,000, and claim 248 contains non-elected modulation of blood cell formation other than hematopoiesis, and claim 249 contains non-elected erythropoietin and granulocyte colony stimulating factor.

Also, in claim 248, the term "including" before each type of blood cell formation such as "hematopoiesis" is suggested to delete.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 247-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 247 lacks an ending step as to how to modulate the blood cell formation in the claimed method. Suggest addition "thereby modulating blood cell formation"; otherwise, the method of claim 247 is considered to be incomplete.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[1] *Written description*

Claims 177-181 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors considered in the Written Description requirement are (1) Actual reduction to practice; (2) Disclosure of drawings or structural chemical formulas; (3) Sufficient relevant identifying characteristics; (4) Method of making the claimed invention; (5) Level of skill and knowledge in the art; and (6) Predictability in the art. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP § 2163.

Actual reduction to practice/Disclosure of drawings or structural chemical formulas

Claim 247 and dependent claims therefrom as written are directed to a method of modulating blood cell formation or hematopoiesis by administering to a subject in need thereof a peptide consisting of SEQ ID NO:27 or 28 which are 193-209 or 193-208 of β-casein, respectively (see the specification at page 76, lines 23-24, and page 101, line 20). Instant specification defines that the "modulating" refers to increasing (stimulating) and decreasing

(inhibiting) frequency, character, duration, outcome, magnitude, cyclic nature, and the like, of a physiological process such as blood cell formation (page 51, lines 8-1). While the specification has describe or provided examples for SEQ ID NO:28 peptide in:(i) stimulating proliferation of GEMM (Granulocyte, Erythroid, Macrophage and Megakaryocyte) colonies (see page 100, lines 22-28), and stimulating total megakaryocyte formation and development in primary murine marrow culture (page 101, lines 19-29); (ii) greatly enhancing the granulopoietic stimulating effects of G-CSF (page 105, lines 15-20, and Fig. 20); (iii) stimulating white blood cell formation such as stimulating early leukocyte growth (page 107, lines 8-17); and (iv) enhancing platelet proliferation/reconstitution (page 108, lines 17-22), the specification fails to describe the β-casein inhibition of the hematopoiesis or blood cell formation. The specification is completely silent is this regard. The relative art does not teach this either. The specification neither provides representative members for inhibiting/reducing hematopoiesis in a subject (genus) which includes a cultured blood cell (in vitro) or a human patient (in vivo), nor describes correlation between the structure (peptide sequence) and function (said "inhibiting"/reducing"). The specification thus need to provide adequate written description and representative species for the genus so as to allow the skilled in the art to recognize that applicant is in possession of the claimed method of inhibiting or inhibiting and stimulating (dual activities) hematopoiesis (claims 247) by administering to a subject (see above) the β-casein peptide consisting of SEQ ID NO:27 or 28 and additionally administering to the subject a blood cell stimulating factor thrombopoietin (claim 249).

Predictability in the art

Since neither the specification nor the art in the relative filed teaches or provided factual indicia for inhibiting the hematopoiesis in a subject in need thereof, the level of unpredictability in the art is high.

Sufficient relevant identifying characteristics

Neither the specification nor the relative art provides factual indicia as to inhibiting or/and (i.e., negatively modulating) hematopoiesis using the β-casein peptide consisting of SEQ ID NO:27 or 28. The "inhibitory" domain or motif has not been disclosed. Thus, the skilled artisan is unable to recognize applicant having procession of the full scope of claimed method.

Level of skill and knowledge in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to use of the β-casein peptide consisting of SEQ ID NO:27 or 28 or use said peptide in combination with the blood cell stimulating factor for inhibiting or inhibiting plus stimulating the hematopoiesis.

The relative art ("*Abstract Search*" (2010, updated) www.faqs.org/abstracts/Zoology-and-wildlife-conservation/Identification-and-characterization-of-an-inhibitor-of-hematopoietic-stem-cell-proliferation.html, page 1-5) teaches it has proved to be very difficult to study the inhibition of blood cells (including blood stem cells) formation or hematopoiesis, because of the lack of an appropriate assay (see page 3, the article *"Growth factors: growth without inflation"* by author: Dexter et al.). This "difficult" renders the level of unpredictability in the art high. This suggests that the level of skill in the art is lower than the required level of disclosure necessary to meet the enablement requirement.

Therefore, claims 247-249 as written fail to satisfy the written description requirement.

[2] *Scope enablement*

Claims 247-249 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while may enable for use of the β-casein peptide consisting of SEQ ID NO:27 or 28 to stimulating or enhancing hematopoiesis in a subject such as stimulating proliferation of Granulocyte, Erythroid, Macrophage and Megakaryocyte (GEMM) colonies, does not reasonably provide enablement for use of said peptide to inhibit or reduce hematopoiesis in a subject in vivo or in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2)The nature of the invention:

Claim 247 and dependent claims therefrom as written are directed to a method of modulating blood cell formation or hematopoiesis by administering to a subject in need thereof a β-casein peptide consisting of SEQ ID NO:27 or 28. Per the specification definition, the "modulating" encompassing increasing (stimulating) and decreasing (inhibiting) blood cell formation (page 51, lines 8-1), i.e., hematopoiesis.

While the specification provides examples for SEQ ID NO:28 peptide in:(i) stimulating proliferation of Granulocyte, Erythroid, Macrophage and Megakaryocyte colonies by SEQ ID NO:28 peptide (page 100, lines 22-28) and stimulating total megakaryocte formation and development (page 101, lines 19-29); (ii) substantially enhancing the granulopoietic stimulating effects of G-CSF (page 105, lines 15-20, and Fig. 20); and (iii) stimulating white blood cell formation such as stimulating early leukocyte growth (page 107, lines 8-17), the specification fails to teach inhibition of the hematopoiesis by the β-casein or SEQ ID NO:27 or 28. The specification neither teaches inhibiting/reducing hematopoiesis in a subject such as a cultured blood cell (in vitro) or a human patient (in vivo). The relative art does not teach this either. Instead, the art teaches that inhibition of the blood cells including blood stem cell proliferation is a difficult task (see page 3, "Abstract search" reference above), suggesting requirement of undue experimentation. As such, the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art:

Since neither the specification nor the art in the relative filed teaches or provided factual indicia for inhibiting the hematopoiesis in a subject in need thereof, the level of unpredictability in the art is high.

(4) The state of the prior art/(5)The quantity of experimentation necessary:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the specification fails to disclose the structural feature common to members of the genus, the specification needs to provide sufficient guidance to be considered enabling for the claimed nucleic acid. In the

absence of working examples or factual evidence with regard to using the β-casein peptide consisiting of SEQ ID NO:27 or 28 to inhibit or reduce the hematopoiesis, unpredictability of the art, the lack of sufficient guidance in the specification in this regard, it would take undue trials and errors to practice the claimed invention. The difficulty of assaying the inhibition of the blood cell formation (see above "*Abstract Search*" reference). This "difficult" renders the quantity of experimentation for screening/characterizing the β-casein peptides having ability of said inhibition or reduction of hematopoiesis large and unpredictable.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide and broad scope of disorders encompassed by the claims. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in molecular biology, entomology as well as knowledge in mutagenesis and microbiology. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. In the absence of teaching or direction regarding the core or consensus sequence(s) critical for the function discussed above, and regarding the structure-function correlation which is missing from instant specification and the art in the related field, an unduly level of skill is needed for the skilled artisan in order to identify inhibitory β-casein peptides which inhibit hematopoiesis.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and

the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

Provisional Claim Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 247 and 248 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of Application of 12764996 ('**996**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 1-3 of 966' disclose a method of inducing or increasing hematopoiesis in a subject comprising administering to said subject caseindin peptide derive from natural casein which comprising the β-casein peptide of SEQ ID NO:27 or 28, which is a common subject matter of instant claims 247 and 248.

Conclusion

No claims are allowed.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

Claim 1 of US Pat. No.7741274 B2 discloses a method of inducing or increasing hematopoiesis in a subject comprising one of an amino acid sequences of SEQ ID NOs: 2-21 and 23-25 which are αS1-peptides (see Figure 3 at page 78 and Figure 26). Since the β-casein peptide consisting of SEQ ID NO:27 or 28 are patentably distinct from said αS1-peptides in structure, claim 1 of 7741274 is not considered to be obvious variation over instant claims 247-249. Thus, US 7741274 is not considered to be an ODP reference herein.

Any comments considered necessary by applicants must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Samuel Wei Liu, Ph.D. whose telephone number is (571) 272-0949. The Examiner can normally be reached daily except alternate Fridays from 8:30 A.M. to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Manjunath N. Rao can be reached at (571) 272-0939. The official fax number for Technology Center 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

/Samuel W. Liu/
Examiner, Art Unit 1656
/ANAND U DESAI/
Primary Examiner, Art Unit 1656
August 1, 2010